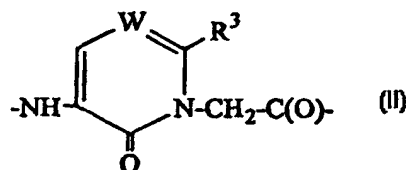
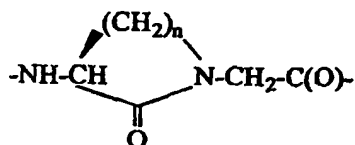




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(54) Title: SERINE PROTEASE INHIBITORS



(57) Abstract

The invention relates to a compound having the formula (I): $\text{R}^1\text{SO}_2\text{-B-X-Z-C(O)-Y}$, B is a bond, an amino acid of the formula $\text{-NH-CH}[(\text{CH}_2)_p\text{C(O)OH}]\text{-C(O)-}$ or an ester derivative thereof wherein p is 1, 2, or 3, Gly, D-1-Piq, D-3-Piq, D-1-Tiq, D-3-Tiq, D-Atc, Aic, or a L- or D-amino acid having a hydrophobic, basic or neutral side chain; X is an amino acid with a hydrophobic side chain, glutamine, serine, threonine, a cyclic amino acid optionally containing an additional heteroatom selected from N, O or S, and optionally substituted with (1-6C)alkyl, (1-6C)alkoxy, benzyloxy or oxo, or X is 2-amino-isobutyric acid, $\text{-NR}^2\text{-CH}_2\text{-C(O)-}$ or the fragment (I) or (II), wherein n is 2, 3, or 4, W is CH or N and R^3 is H, (1-6C)alkyl or phenyl which groups may optionally be substituted with hydroxy, (1-6C)alkoxy, COOH, COO(1-6C)alkyl, CONH₂, or halogen; Z is lysine or 4-aminocyclohexylglycine. The compounds of the invention have anticoagulant activity and can be used in treating or preventing thrombin-related diseases. The variable R^1 and Y are defined in claim 1.

Table 44 : Characterization (retention time on reversed phase HPLC and M+H peak in electrospray mass spectrometry) of EtSO₂-B-X-LysΨ[COCO]-O-iPropyl prepared on Hydroxymethyl-resin. HPLC conditions : Flow : 1.0 mL/min ; Buffers A : water, B :

- 5 acetonitril/water (6/4 v/v), C : 0.5 M phosphate-buffer pH = 2.1 ; Gradient : 0 → 45 min 65 % A/15 % B/20 % C → 0 % A/80 % B/20 % C. UV-detection at 210 nm.

	B				
	Asn	D-Leu	D-Phe	Nal	D-3-Tiq
EtSO ₂ -B-D-Leu-D/L- LysΨ[COCO]-O-iPropyl	Rt = 17.07 min M+H = 536.4	Rt = 27.20 min M+H = 535.6	Rt = 30.89 min M+H = 569.4	Rt = 38.17 min M+H = 619.6	Rt = 33.54 min M+H = 581.4
EtSO ₂ -B-Leu-D/L- LysΨ[COCO]-O-iPropyl	Rt = 17.17 min M+H = 536.4	Rt = 30.78 min M+H = 535.6	Rt = 32.89 min M+H = 569.4	Rt = 37.79 min M+H = 619.6	Rt = 33.60 min M+H = 581.4
EtSO ₂ -B-Gln-D/L- LysΨ[COCO]-O-iPropyl	Rt = 5.40 min M+H = 551.2	Rt = 15.74 min M+H = 550.4	Rt = 18.05 min M+H = 584.4	Rt = 28.44 min M+H = 634.4	Rt = 21.27 min M+H = 596.4
EtSO ₂ -B-Phe-D/L- LysΨ[COCO]-O-iPropyl	Rt = 20.75 min M+H = 570.4	Rt = 33.33 min M+H = 569.4	Rt = 35.18 min M+H = 603.4	Rt = 39.47 min M+H = 653.6	Rt = 35.92 min M+H = 615.6

10 **Example 45.**

The following compounds can be prepared by using the methods of the present invention:

CF₃SO₂-D-Cha-Pro-LysΨ[COCO]-O-iPropyl

MeSO₂-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

n-ButylSO₂-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

- 15 CF₃SO₂-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

BzlSO₂-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

EtSO₂-D-(p-OEt-Phe)-Pro-LysΨ[COCO]-O-iPropyl

EtSO₂-D-Nle-Pro-LysΨ[COCO]-O-iPropyl

EtSO₂-D-Cha-Azt-LysΨ[COCO]-O-iPropyl

- 20 EtSO₂-D-Cha-(N-cyclopentyl-Gly)-LysΨ[COCO]-O-iPropyl

EtSO₂-D-Cha-Val-LysΨ[COCO]-O-iPropyl

- EtSO₂-D-Cha-Pec-LysΨ[COCO]-O-iPropyl
EtSO₂-D-Cha-(3,4-dehydro-Pro)-LysΨ[COCO]-O-iPropyl
EtSO₂-D-Cha-Pro-LysΨ[COCO]-Azetidine
MeSO₂-D-Cha-Pro-LysΨ[COCO]-Azetidine
5 n-ButylSO₂-D-Cha-Pro-LysΨ[COCO]-Azetidine
CF₃SO₂-D-Cha-Pro-LysΨ[COCO]-Azetidine
BzlSO₂-D-Cha-Pro-LysΨ[COCO]-Azetidine
[3-(BzlSO₂amino)-2-oxo-1,2-dihydropyridinyl]-acetyl-LysΨ[COCO]-Azetidine
[3-(BzlSO₂amino)-6-methyl-2-oxo-1,2-dihydropyridinyl]-acetyl-LysΨ[COCO]-Azetidine
10 MeSO₂-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl
n-ButylSO₂-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl
CF₃SO₂-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl
BzlSO₂-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl
EtSO₂-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl
15 MeSO₂-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl
n-ButylSO₂-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl
CF₃SO₂-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl
BzlSO₂-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl
EtSO₂-D-Tyr(Et)-Pro-AcgΨ[COCO]-O-iPropyl
20 EtSO₂-D-Nle-Pro-AcgΨ[COCO]-O-iPropyl
EtSO₂-D-Cha-Azt-AcgΨ[COCO]-O-iPropyl
EtSO₂-D-Cha-(N-cyclopentyl-Gly)-AcgΨ[COCO]-O-iPropyl
EtSO₂-D-Cha-Val-AcgΨ[COCO]-O-iPropyl
EtSO₂-D-Cha-Pec-AcgΨ[COCO]-O-iPropyl
25 EtSO₂-D-Cha-(3,4-dehydro-Pro)-AcgΨ[COCO]-O-iPropyl
EtSO₂-D-Cha-Pro-AcgΨ[COCO]-Azetidine
EtSO₂-D-Tyr(Me)-Pro-AcgΨ[COCO]-Azetidine
EtSO₂-D-Tyr(Me)-Pro-AcgΨ[COCO]-NH₂
MeSO₂-D-Cha-Pro-AcgΨ[COCO]-Azetidine
30 n-ButylSO₂-D-Cha-Pro-AcgΨ[COCO]-Azetidine
CF₃SO₂-D-Cha-Pro-AcgΨ[COCO]-Azetidine